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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,653	COLEMAN ET AL.	
	Examiner	Art Unit	
	JENNIFER DUNSTON	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,57,60 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,57,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/20/2009 has been entered.

Receipt is acknowledged of an amendment, filed 3/20/2009, in which claims 58-59 were canceled, claims 1 and 57 were amended, and claim 61 was newly added. Claims 1, 57, 60 and 61 are pending.

Priority

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120 and 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after

November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required.

Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

The reference submitted within the time period set forth in 37 CFR 1.78(a) indicated that this application is a continuation of U.S. Serial No. 09/178,170 filed January 25, 2001, which is a continuation of U.S. Serial No. 09/178,170, filed October 23, 1998, which claims the benefit of U.S. Serial No. 60/063,274 and U.S. Serial No. 60/179,214. This reference was submitted on the application transmittal letter, filed 4/9/2004, and as an amendment to the specification, filed 4/9/2004. Acknowledgement of this priority claim was made in the first filing receipt. In the reply filed 3/20/2009, the first sentence(s) of the specification were amended to indicate that the present application is a continuation-in-part of U.S. Serial No. 09/770,534, filed January 25, 2001, which is a continuation of U.S. Serial No. 09/178,170, filed October 23, 1998, which claims the benefit of U.S. Serial No. 60/063,274, filed on October 24, 1997. However, the reference to 09/770,534 was not provided within the time period set forth in 37 CFR 1.78(a). The first reference to 09/770,534 occurs in the request for corrected official filing receipt, filed 12/27/2004. This reference was not submitted within four months from the actual filing date of the instant application or sixteen months from the filing date of the prior-filed application.

Response to Arguments - Priority

The response notes that the priority claim is now in the first sentence of the specification. Further, the response asserts that the amendment to the specification, filed 3/20/2009, to delete any benefit claim to provisional Application No. 60/179,214 is proper, because deletion of a

claim for priority is not a claim for benefit. Thus, Applicant asserts the present amendment is not a late claim for benefit and does not require a petition under 37 CFR 1.78(a).

Although the claim for priority is now in the first sentence(s) of the specification, priority to Application No. 09/770,534 was not claimed within the time period set forth in 37 CFR 1.78(a). As noted in the petition decision mailed, 9/11/2007, Applicant may submit a renewed petition under 37 CFR §§ 178(a)(3) and 1.78(a)(6), along with an amendment or Application Data Sheet that complies with the provisions with 37 CFR 1.121 that overcomes the noted problems with the claim for priority. Applicant has not filed a renewed petition under 37 CFR §§ 178(a)(3) and 1.78(a)(6) that has been granted.

The response notes that on April 9, 2004, the day the present application was filed, a preliminary amendment was filed. The response asserts that, as of that day, the information contained within the preliminary amendment was considered part of the application as filed. Further, the response asserts that a specific reference was made to each application within the present amended claim to priority. The response asserts that this understanding is supported by the PTO's issuance of a corrected filing receipt based on the correction of the obvious error of duplicate application numbers in the priority chain, which evidences the PTO's understanding to same. The response asserts that the first recitation of 09/178,170 clearly is understood as an obvious error because the date is correct and is recited as a continuation of application of 09/178,170. Moreover, the response asserts that there is only one application "having these characteristics easily identifiable in the patent office.

First, it is noted that the instant application was filed before September 21, 2004. A preliminary amendment filed on the filing date of the application is only part of the original

disclosure of the application if the preliminary amendment was referred to in the first executed oath or declaration under 37 CFR 1.63 filed in the application. In the instant case, the preliminary amendment was not referred to on the first executed oath or declaration under 37 CFR 1.63 filed in the application.

Second, it is noted that the claim to priority in the preliminary amendment, filed 4/9/2004, does not contain a specific reference to each application to which priority is now claimed. The preliminary amendment referred only to Application Nos. 09/178,170, 60/063,274 and 60/179,214. Second, the request for a corrected filing receipt was filed 12/27/2004, which is more than four months after the filing of the instant application and more than sixteen months after the filing of the parent application. While prompt review of a filing receipt and correction can be used to avoid the need to file a petition under 37 CFR 1.78, Applicant did not submit the request for a corrected filing receipt within the time set forth in 37 CFR 1.78(a). Thus, the corrected filing receipt does not obviate the need for filing a petition. Further, the office recognizes that the reference to Application No. 09/770,534 was not present on the filing date of the instant application. Page 3 of the petition decision, mailed 9/11/2007, indicates that it is improper to incorporate by reference prior-filed Application No. 09/770,534 in the first sentence of the specification. The petition decision states, "When a benefit claim under 35 U.S.C. § 120 is submitted after the filing of an application, the reference to the prior application cannot include an incorporation by reference statement of the prior application." Thus, the Office recognizes that the preliminary amendment, filed on the filing date of the instant application, did not make reference to Application No. 09/770,534.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: the present application was filed with a copy of the oath or declaration from prior nonprovisional Application No. 09/178,170. The first sentences of the specification now indicate that the present application is a continuation-in-part of Application No. 09/770,534, which is a continuation of Application No. 09/178,170. A newly executed oath or declaration must be filed in any continuation-in-part application. See 37 CFR 1.63(e).

Specification

The disclosure is objected to because of the following informalities: the description of the drawings and table are not consistent throughout the specification.

The brief description of the drawings states that Figure 1 depicts a schematic presentation of the single cell approach to mRNA profiling. However, page 50, lines 29-31 state that it is evident in Figure 1A that hybridization intensity is influenced by two factors, the amount of the aRNA probe used and that of plasmid DNA immobilized on the filter. The paragraph goes onto state that one should compare 0.5-kb synthetic λ RNA in blots c and d of Figure 1A and that Figure 1B shows that the specific signal is linearly related to the RNA concentration between 0.2 and 120 nm for all three RNA species. These features are not shown in Figure 1, and there are no panels labeled Figure 1A and 1B.

The brief description of the drawings states, "Figure 2 is a photomicrograph of the CA1 hippocampal region of an AD case demonstrating neurons containing NFT neurons (arrowheads), and NFT-free neurons (arrows)." This description is consistent with what is

shown in Figure 2. However, page 51, lines 23-24 state that "FIG. 2 shows that the average of all the measurements is linear to the amount of radiolabeled a RNA used in the assay (r^2 = 0.992)." This statement refers to gene expression measurements for early- and late-stage AD brain samples, which is not shown in Figure 2.

The brief description of the drawings states that Figure 3 shows "the separation of cell population from five brains by canonical analysis. The first canonical variable was plotted against the second canonical variable for each cell. Cells from AD brains are filled with symbols, and cells from control brains are open symbols." These statements are not consistent with the content of Figure 3. Figure 3 shows points that refer to five brains classified as Late and Early AD. All brains are AD brains, including brains with open symbols. Furthermore, the colors referred to at page 34 cannot be seen in the black and white drawings. The specification also discusses Figure 3 at the paragraph bridging pages 51-52 of the specification and the paragraph bridging pages 53-54. This portion of the specification refers to Figure 3 as showing differences in gene expression between early- and late-stage AD brains as a percent difference for cyclin D1, HSP27, GAD, wee1, and α1-Act. These gene expression differences are not shown in Figure 3.

The brief description of the drawings describes Figure 4A as showing the results of combined immunohistochemistry/*in situ* hybridization for synaptophysin messages. This is consistent with what is shown in Figure 4A. However, page 52, lines 25-26 assert that Figure 4A shows data from single neurons from CA1 subiculum of five brains, which were analyzed by comparing cells from brains at early- and late-stage AD using canonical analysis. The information shown in Figure 4A does not represent a canonical analysis of gene expression data.

The brief description of the drawings describes Figure 4B as showing the results of combined immunohistochemistry/*in situ* hybridization for poly A+ message. However, at the sentence bridging pages 52-53, the specification states, "The influence of each cDNA on canonical variable 1 is presented graphically (FIG. 4B). These features are not shown in Figure 4B.

The brief description of the drawings describes Figure 4C as showing the results of combined immunohistochemistry/*in situ* hybridization for cathepsin D message. However, page 53, lines 6-9 describe Figure 4C as showing the results of a canonical analysis with five groups. These features are not shown in Figure 4C.

The brief description of the drawings describes Figure 4D as showing synaptophysin grain density in tangle neurons relative to nontangle neurons. However, page 53, lines 9-11 assert that FIG. 4D shows the influence of each cDNA on canonical 1 in the five-group analysis. This information is not shown in Figure 4D.

The brief description of the drawings state that Figure 5 shows double immunocytochemistry combined with *in situ* hybridization. However, page 53, lines 22-29 refers to FIG. 5A, 5B and 5C, which are not shown in the drawings.

At page 24, Table 1 shows preferred probes for *in situ* and immunohistochemistry studies. However, page 44 states that Table 1 shows the average of data points in duplicate for each cDNA of α1-ACT, GAPDH, CamK II, cyclin D1, and nestin. This data is shown in Table 2. It would be remedial to amend page 44, line 14 to refer to Table 2 rather than Table 1. At page 45, lines 8-12 the specification states that the information on the tissues used in the study are summarized in Table 1. This information is not present in Table 1. At page 53, the

specification refers to Table 1 as showing that the samples used to validate results seen with the aRNA method, ISH was performed with samples that were not necessarily from the same individuals used for the aRNA analysis. This information is not shown in Table 1.

Appropriate correction is required.

The use of the trademarks GENBANK (page 25, lines 2, 18, 27 and 31; page 37, line 29; page 46, line 27; page 48, line 19), SUPERSCRIPT (page 46, line 4), and TRIZOL (page 47, line 9) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Drawings

The drawings are objected to because Figures 8 and 9 are illegible and will not reproduce well. The figures are black boxes that do not show the details described in the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be

renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Response to Arguments - Claim Objections

The objection of claims 1 and 57 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 3/20/2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 57, 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made over claims 1 and 57-60 in the Office action mailed 10/5/2007 and has been rewritten to address the amendments to the claims in the reply filed 3/20/2009.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 1 is drawn to a "method of profiling mRNA production during stages." The method is drawn to the steps of (i) isolating a plurality of cells from a subject, wherein the subject is human; (ii) analyzing the mRNA production in the cells from the subject, wherein the mRNA encode two or more genes selected from the group consisting of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1; (iii) quantitating the levels of the mRNA; and (iv) comparing the levels of mRNA in the subject to a control, wherein the subject is in need of diagnosis of Alzheimer's disease. Claim 57 limits the genes to two or more genes selected from the group consisting of α1-ACT, cyclin D1, HSP27 and wee1. Claim 60 limits the sample of the method of claim 1 to a blood sample collected from a living patient. Claim 61 limits the sample of the method of claim 57 to a blood sample collected from a living patient.

The nature of the invention is complex in that the gene expression levels must be indicative of the diagnosis or staging of Alzheimer's disease—the only disclosed use for the claimed invention.

Breadth of the claims: The claims are broad in that they encompass any type of sample, and any increase or decrease in expression of the recited combinations of genes. Further, the claims are broad in that they encompass every possible combination of two or more genes selected from the group consisting of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1. The

phrase "during stages" in the preamble broadly encompasses the comparison of any stages of Alzheimer's disease (no disease, early disease, late disease etc.). Thus, the method broadly encompasses the diagnosis of Alzheimer's disease at any stage by comparison of the gene expression with any control of any stage of Alzheimer's. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

The claims refer to mRNA molecules that encode genes. However, mRNA is encoded by genes (e.g., specification, page 28, line 30). The genes or mRNA encode the proteins (e.g., specification, page 54, line 17).

Guidance of the specification and existence of working examples: The specification envisions the comparison of gene expression profiles for the diagnosing or monitoring the progression of a disease (e.g., pages 18-19). The specification envisions using any sample from a living patient, including brain tissue (from a living individual or postmortem), blood, cheek scrapings, cerebral spinal fluid, saliva, urine, and skin (e.g., page 22, lines 3-4; page 27, lines 8-10). The specification envisions the diagnosis or monitoring of virtually any disease: infections by bacteria, fungi, or viruses, genetic disease, autoimmune disease, and degenerative disease such as Alzheimer's disease (e.g., page 28, lines 8-13).

The working examples of the specification teach the analysis of gene expression of twenty genes in neurons sampled from early and late stage Alzheimer's disease (AD) of post mortem AD brains (e.g., page 47, lines 16-21). Seven cells were tested in duplicate for each brain and two early AD and three late AD brains were tested (e.g., page 47, lines 16-21; page 51, lines 17-20). When multivariate canonical discriminant analysis with was used with two groups delineated, the brains were defined as either late- or early-stage AD brain (e.g., paragraph

bridging pages 47-48). The canonical variable 1 represents the weighted combination of cDNAs that best distinguish the cells as being from early- or late-stage AD brain (e.g., page 52, lines 29-30). This analysis was performed with all 20 cDNAs. Using ANOVA, five genes were found to be significantly different between the two groups: α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1 ($p<0.05$) (e.g., paragraph bridging pages 51-52). The specification asserts that cyclin D1, HSP27, and GAD were significantly decreased in late stage AD while α1-ACT and wee1 were significantly increased in late AD (e.g., paragraph bridging pages 51-52). The specification notes that the genes contributing heavy weights to canonical variable 1, either positive or negative, are not necessarily the genes with significant changes in expression identified by ANOVA (e.g., page 53, lines 1-3). The specification states that the top five genes with the heaviest weights to canonical variable 1 are CREB, cyclin D1, wee1. NF-M, and crystallin (e.g., page 53, lines 4-5). This section of the specification refers to a table and figures that do not appear to be present in the instant specification, making the analysis of the data difficult. Specifically, the description of Figures 1-5 and Table 1 in this section does not match what is shown in the drawings of the specification or Table 1 at page 24 of the specification.

The specification does not teach the expression levels of these genes in individuals without AD. The specification does not teach the expression level of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1 in any sample other than neurons from human postmortem brain.

No working examples are provided where as few as two genes are used to classify a subject as having or not having AD or as having a particular stage of AD.

Predictability and state of the art: The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes

of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess. Annals of Oncology, Vol. 15, pages 1731-1737, 2004, cited in a prior action; e.g., paragraph bridging pages 1732-1733). In the instant case, the specification uses gene expression analysis to identify genes that are differentially expressed in neurons from a small sample of postmortem AD brains. Thus, the specification uses the gene expression analysis as a screening tool to identify genes or provide insight into AD. However, the claims are drawn to using gene expression analysis to either diagnose or monitor any disease from any subject in any sample type. Pusztai and Hess teach that validation of gene expression important to biological function may be validated by using different methods, such as RT-PCR, whereas the most appropriate validation for using gene expression analysis as a classification tool is testing the predictor on independent sets of cases (e.g., page 1733, left column, 1st full paragraph). In the instant case the specification does not teach the predictive value of the mRNA expression for the gene combinations recited in the claims for the classification of any individual into any disease stage of Alzheimer's disease. The post filing art teaches that the use of biomarkers to diagnose AD is still an underdeveloped area (DeKosky, ST. CNS Sepctr. Vol. 13, No. 3 (Suppl 3), pages 7-10, March 2008). DeKosky teaches that peripheral markers of AD, such as white blood cell patterns of RNA expression, may serve as a specific diagnostic test, a presymptomatic test, a surrogate indication of disease severity, or a surrogate indication of therapeutic effectiveness (e.g., page 8, right column, last full paragraph). However, DeKosky states, "Thus far, no validated tests for any of these functions is available." See page 8, right column, last sentence of last full paragraph). DeKosky provides an example as to why the tests

are not available with specific reference to plasma $A\beta_{42}$ levels (e.g., paragraph bridging pages 8-9). DeKosky teaches that while expression differences may distinguish patients with AD from controls as a group, the variability of gene expression levels precludes the use of the diagnostic markers on an individual basis (e.g., paragraph bridging pages 8-9). DeKosky teaches that biomarker studies that search for differences in levels of a particular protein or proteins between AD patients in controls may contribute to hypotheses about biological changes that occur in the disease; however, biomarkers often yield only probabilistic data when confirming a specific diagnosis of mild cognitive impairment or AD (e.g., page 10, left column, 1st full paragraph).

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001, cited in a prior action) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group being tested (e.g., page 1734, paragraph bridging columns; Table 1). The instant specification teaches that a major source of variation in gene expression levels is the method of detection

(62%), yet within- and between-sample variation does exist (e.g., paragraph bridging pages 33-34).

Genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined (Kroese et al. Genetics in Medicine, Vol. 6, pages. 475-480, 2004, cited in a prior action). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g., page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g., page 479, 2nd column, last paragraph).

Even within AD, the expression of the recited genes is not necessarily consistent. For example, Renkawek et al (Acta Neuropathol, Vol. 87, pages 511-519, 1994, cited in a prior action) teach that heat-shock protein 27 (hsp27) is expressed to a greater extent in late AD as compared to control brains and patients with shorter dementia (e.g., pages 514-515, Expression of hsp 27 in AD-affected brains). This contrasts with the teachings of the specification. The specification asserts that HSP27 is decreased in late AD as compared to early AD (e.g., paragraph bridging pages 51-52). Accordingly, it would be unpredictable to extrapolate the gene expression results of the specification to classify individuals. Furthermore, it would be unpredictable to extrapolate the expression results to other cell types and other diseases.

Amount of experimentation necessary: Given the lack of guidance in the specification and prior art with regard to diagnosing or staging AD using the mRNA expression levels of the claimed combination of genes, the quantity of experimentation in this area is very large. Due to the small sample sizes used and the use of only neurons from only early and late AD postmortem brain, one would not know how to use the claimed invention for the diagnosis or staging of AD from a sample obtained from a living subject. The nature of the guidance in the specification is not specific enough to allow one to practice the claimed invention for the analysis of any stage of AD. For one to use the claimed invention, one would be required to perform a large amount of experimentation, with the success of one combination of genes for one particular stage not providing any guarantee of success with any other stage.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 57, 60 and 61 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

The rejection of claims 58 and 59 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 3/20/2009.

With respect to the rejection of claims 1, 57, 60 and 61 under 35 U.S.C. 112, first paragraph, Applicant's arguments filed 3/20/2009 have been fully considered but they are not persuasive.

The response asserts that the amendments to the claims to limit the disease to Alzheimer's disease and to limit the subject to a human overcomes the rejection of record, which was interpreted as focusing on the breadth of the claims. Further, the response asserts that the Examiner points out that the specification provides sufficient enablement for Alzheimer's disease in humans at page 7, lines 9-11 of the Office action mailed 10/5/2007.

These arguments are not found persuasive. The claims are still broad with regard to the use of any sample, such as brain tissue, blood, cheek scrapings, cerebral spinal fluid, urine and skin, and the use of any control (no AD, early-stage AD, late-stage AD, etc.). Page 7, lines 9-11 of the Office action mailed 10/5/2007, states, "The working examples of the specification teach the analysis of gene expression of twenty genes in neurons sampled from early and late stage Alzheimer's disease (AD) of postmortem AD brains (e.g., page 47, lines 16-21). It would be within the skill of the art to perform the steps of (i) isolating a plurality of cells from a human subject; (ii) analyzing mRNA production in the cells from the subject, wherein the mRNA encode two or more proteins selected from the group consisting of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1; (iii) quantitating the levels of the mRNA; and (iv) comparing the levels of the mRNA in the subject to a control. However, the claim requires the subject to be in need of a diagnosis of Alzheimer's disease, and the only disclosed use for the method is the diagnosis or staging of Alzheimer's disease. Thus, the method requires the use of the gene expression analysis to categorize a subject as having or not having Alzheimer's disease. As noted on pages 8-10 of the Office action mailed 10/5/2007, the use of gene expression analysis as a classification tool is unpredictable, especially when a small number of samples are used. The specification does make mention of the use of the gene expression levels in canonical discriminant analysis

with two groups delineated, where the brains were defined as either late- or early-stage AD brain (e.g., paragraph bridging pages 47-48). However, the details of this analysis are unclear, because the specification refers to Figures and tables whose description in the Examples is not consistent with what is shown in the specification (see the objection to the specification above). This analysis was not performed with as few as two genes as now claimed. Furthermore, the examples of the specification are not working examples of the claimed invention in they deal with the comparison of groups, whereas the claim is drawn to the analysis of an individual subject. There is no evidence that the gene expression levels obtained from one individual as compared to one control would be diagnostic for AD. The post filing art teaches that the use of biomarkers to diagnose AD is still an underdeveloped area (DeKosky, ST. CNS Sepctr. Vol. 13, No. 3 (Suppl 3), pages 7-10, March 2008). DeKosky teaches that peripheral markers of AD, such as white blood cell patterns of RNA expression, may serve as a specific diagnostic test, a presymptomatic test, a surrogate indication of disease severity, or a surrogate indication of therapeutic effectiveness (e.g., page 8, right column, last full paragraph). However, DeKosky states, "Thus far, no validated tests for any of these functions is available." See page 8, right column, last sentence of last full paragraph). DeKosky provides an example as to why the tests are not available with specific reference to plasma $A\beta_{42}$ levels (e.g., paragraph bridging pages 8-9). DeKosky teaches that while expression differences may distinguish patients with AD from controls as a group, the variability of gene expression levels precludes the use of the diagnostic markers on an individual basis (e.g., paragraph bridging pages 8-9). DeKosky teaches that biomarker studies that search for differences in levels of a particular protein or proteins between AD patients in controls may contribute to hypotheses about biological changes that occur in the

disease; however, biomarkers often yield only probabilistic data when confirming a specific diagnosis of mild cognitive impairment or AD (e.g., page 10, left column, 1st full paragraph). In other words, definitive diagnosis of AD using biomarkers, such as blood biomarkers, is a technique of the future. Undue experimentation would be required to determine how to use the gene expression levels of each combination of claimed mRNA to result in the diagnosis or staging of AD.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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